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(57) Abstract

The present application provides a series of benzimidazole compounds which inhibit the growth of picornaviruses, such as rhinoviruses, enteroviruses, polioviruses, coxsackieviruses of the A and B groups, echo virus and Mengo virus and flaviviruses such as hepatitis C and bovine diarrheal virus.

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ANTI-VIRAL COMPOUNDS

The present invention is in the field of human medicine, particularly in the treatment of viral infections. More particularly, the present invention relates to the treatment of rhinoviral, enteroviral and flaviviral inventions.

The incidence of viral upper respiratory disease, the common cold, is immense. It has been estimated that nearly a billion cases annually appear in the United States alone. Rhinovirus, a member of the picornaviridae family, is the major cause of the common cold in humans. Because more than 110 strains of rhinoviruses have been identified, the development of a practical rhinovirus vaccine is not feasible, and chemotherapy appears to be the more desirable approach. Another member of the picornavirus family is the enterovirus, which includes approximately eighty human pathogens. Many of these enteroviruses cause cold-like symptoms; others can cause more serious diseases such as polio, conjunctivitis, aseptic meningitis and myocarditis.

Illness related to rhinovirus infection is evidenced by nasal discharge and obstruction. Furthermore, it has been implicated in otitis media, predisposes the development of bronchitis, exacerbates sinusitis, and has been implicated in the precipitation of asthmatic altoclis. Although it is considered by many to be a mere nuisance, its frequent occurrence in otherwise healthy individuals and the resulting economic importance in terms of employee absenteeism and physician visits have made it the subject of extensive investigation.

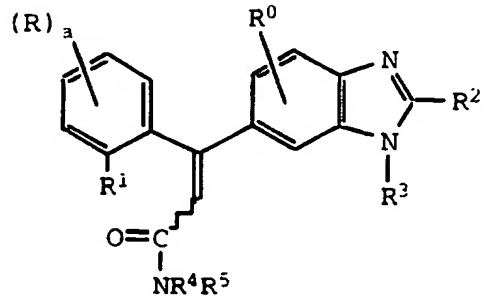
The ability of chemical compounds to suppress the growth of viruses in vitro may be readily demonstrated using a virus plaque suppression test or a cytopathic effect test (CPE). Cf Siminoff, Applied Microbiology, 9(1), 66 (1961). Although a number of chemical compounds that inhibit picornaviruses such as rhinoviruses have been identified, many are unacceptable due to 1) limited spectrum of activity, 2) undesirable side effects or 3) inability to

prevent infection or illness in animals or humans. See Textbook of Human Virology, edited by Robert B. Belshe, chapter 16, "Rhinoviruses," Roland A. Levandowski, 391-405 (1985). Thus, despite the recognized therapeutic potential associated with a rhinovirus inhibitor and the research efforts expended thus far, a viable therapeutic agent has not yet emerged. For example, antiviral benzimidazole compounds have been disclosed in U.S. Pat. Ser. Nos. 4,008,243, 4,018,790, 4,118,573, 4,118,742, 4,174,454 and 4,492,708.

In general, the compounds disclosed in the above patents do not have a desirable pharmacological profile for use in treating rhinoviral infections. Specifically, these compounds do not possess satisfactory oral bioavailability or a high enough inhibitory activity to compensate for their relatively low oral bioavailability to permit their widespread use. In addition, it is widely accepted in the art that compounds used to treat rhinoviral infections should be very safe from a toxicological standpoint.

Accordingly, it is a primary object of this invention to provide novel benzimidazole compounds which inhibit the growth of picornaviruses, such as rhinoviruses, enteroviruses such as polioviruses, coxsackieviruses of the A and B groups, or echo virus and which have a desirable pharmacological profile..

The present invention provides compounds of formula I



I

wherein:

a is 0, 1, 2 or 3;

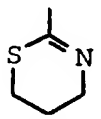
each R is independently hydrogen, halo, cyano, amino, halo(C_1-C_6)alkyl, di(C_1-C_4)alkylamino, azido, C_1-C_6 alkyl, carbamoyl, carbamoyloxy, carbamoylamino, C_1-C_6 alkoxy, C_1-C_4 alkylthio, C_1-C_4 alkylsulfinyl, C_1-C_4 alkylsulfonyl, pyrrolidino, piperidino or morpholino;

R^0 is hydrogen, halo, C_1-C_4 alkyl or C_1-C_4 alkoxy;

R^1 is halo, cyano, hydroxy, methyl, ethyl, methoxy, ethoxy, methylthio, methylsulfinyl or methylsulfonyl;

R^2 is hydrogen, amino or -NHC(O)(C_1-C_6 alkyl);

R^3 is dimethylamino, C_1-C_{10} alkyl, C_3-C_7 cycloalkyl, substituted C_3-C_7 cycloalkyl, halo(C_1-C_6)alkyl, phenyl, substituted phenyl, furyl, thienyl, thiazolyl, thiazolidinyl, pyrrolidino, piperidino, morpholino or a group of the formula:



;

R^4 and R^5 are independently hydrogen or C_1-C_4 alkyl;

or a pharmaceutically acceptable salt thereof.

The present invention also provides pharmaceutical formulations comprising a compound of the present invention, or a pharmaceutically acceptable salt thereof, in combination with a pharmaceutically acceptable carrier, diluent or excipient therefor.

The present invention also provides a method for inhibiting a picornavirus comprising administering to a host in need thereof, an effective amount of a compound of formula I, or a pharmaceutically acceptable salt thereof, wherein a, R, R^0, R^1, R^2, R^3, R^4 and R^5 are as defined above.

The present invention also provides a method for inhibiting a flavivirus comprising administering to a host in need thereof, an effective amount of a compound of formula I, or a pharmaceutically acceptable salt thereof, wherein a, R, R^0, R^1, R^2, R^3, R^4 and R^5 are as defined above.

All temperatures stated herein are in degrees Celsius (°C). All units of measurement employed herein are in weight units except for liquids which are in volume units.

As used herein, the term "C_1-C_{10} alkyl" represents a straight or branched alkyl chain having from one to ten carbon atoms. Typical C_1-C_{10} alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, *sec*-butyl, *t*-butyl, pentyl, *neo*-pentyl, hexyl, 2-methylhexyl, heptyl and the like. The term "C_1-C_{10} alkyl" includes within its definition the terms "C_1-C_6 alkyl" and "C_1-C_4 alkyl."

"Halo" represents chloro, fluoro, bromo or iodo.

"Halo(C_1-C_6)alkyl" represents a straight or branched alkyl chain having from one to six carbon atoms with 1, 2 or 3 halogen atoms attached to it. Typical halo(C_1-C_6)-alkyl groups include chloromethyl, 2-bromoethyl, 1-chloroisopropyl, 3-fluoropropyl, 3-bromobutyl, 3-chloroisobutyl, iodo-*t*-butyl, trichloromethyl, trifluoromethyl, 2,2-chloro-iodoethyl, 2,3-dibromopropyl and the like.

"C_1-C_4 alkylthio" represents a straight or branched alkyl chain having from one to four carbon atoms attached to a sulfur atom. Typical C_1-C_4 alkylthio groups include methylthio, ethylthio, propylthio, isopropylthio, butylthio and the like.

"C_1-C_6 alkoxy" represents a straight or branched alkyl chain having from one to six carbon atoms attached to an oxygen atom. Typical C_1-C_6 alkoxy groups include methoxy, ethoxy, propoxy, isopropoxy, butoxy and the like. The term "C_1-C_6 alkyl" includes within its definition the term "C_1-C_4 alkyl."

"Di(C_1-C_4)alkylamino" represents two straight or branched alkyl chains having from one to four carbon atoms attached to a common amino group. Typical di(C_1-C_4)alkyl-amino groups include dimethylamino, ethylmethylamino, methylpropylamino, ethylisopropylamino, butylmethylamino, *sec*-butylethylamino and the like.

"C_1-C_4 alkylsulfinyl" represents a straight or branched alkyl chain having from one to four carbon atoms attached to a sulfinyl moiety. Typical C_1-C_4 alkylsulfinyl groups include methylsulfinyl, ethylsulfinyl, propyl-sulfinyl, isopropylsulfinyl, butylsulfinyl and the like.

"C_1-C_4 alkylsulfonyl" represents a straight or branched alkyl chain having from one to four carbon atoms attached to a sulfonyl moiety. Typical C_1-C_4 alkylsulfonyl groups include methylsulfonyl, ethylsulfonyl, propyl-sulfonyl, isopropylsulfonyl, butylsulfonyl and the like.

"Substituted phenyl" represents a phenyl ring substituted with 1-3 substituents selected from the following: halo, cyano, C_1-C_4 alkyl, C_1-C_4 alkoxy, amino or halo(C_1-C_4)alkyl.

"Substituted C_3-C_7 cycloalkyl" represents a cycloalkyl ring substituted with 1-3 substituents selected from the following: halo, cyano, C_1-C_4 alkyl, C_1-C_4 alkoxy, amino or halo(C_1-C_4)alkyl.

The claimed compounds can occur in either the cis or trans conformation. For the purposes of the present application, cis refers to those compounds where the carboxamide moiety is cis to the benzimidazole ring and trans refers to those compounds where the carboxamide moiety is trans to the benzimidazole ring. Both isomers are included in the scope of the claimed compounds.

As mentioned above, the invention includes the pharmaceutically acceptable salts of the compounds defined by formula I. A compound of this invention can possess a sufficiently acidic, a sufficiently basic, or both functional groups, and accordingly react with any of a number of inorganic bases, and inorganic and organic acids, to form a pharmaceutically acceptable salt.

The term "pharmaceutically acceptable salt" as used herein, refers to salts of the compounds of the above formula which are substantially non-toxic to living organisms. Typical pharmaceutically acceptable salts

include those salts prepared by reaction of the compounds of the present invention with a mineral or organic acid or an inorganic base. Such salts are known as acid addition and base addition salts.

Acids commonly employed to form acid addition salts are inorganic acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, phosphoric acid, and the like, and organic acids such as *p*-toluenesulfonic, methanesulfonic acid, ethansulfonic acid, oxalic acid, *p*-bromophenylsulfonic acid, carbonic acid, succinic acid, citric acid, benzoic acid, acetic acid, and the like.

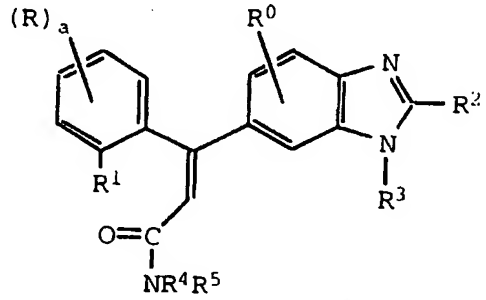
Examples of such pharmaceutically acceptable salts are the sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, chloride, bromide, iodide, acetate, propionate, decanoate, caprylate, acrylate, formate, isobutyrate, caproate, heptanoate, propiolate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, butyne-1,4-dioate, hexyne-1,6-dioate, benzoate, chlorobenzoate, methylbenzoate, dinitrobenzoate, hydroxybenzoate, methoxybenzoate, phthalate, sulfonate, xylenesulfonate, phenylacetate, phenylpropionate, phenylbutyrate, citrate, lactate, γ-hydroxybutyrate, glycollate, tartrate, methanesulfonate, ethanesulfonate, propanesulfonate, naphthalene-1-sulfonate, napththalene-2-sulfonate, mandelate and the like. Preferred pharmaceutically acceptable acid addition salts are those formed with mineral acids such as hydrochloric acid and sulfuric acid, and those formed with organic acids such as maleic acid and methanesulfonic acid.

Base addition salts include those derived from inorganic bases, such as ammonium or alkali or alkaline earth metal hydroxides, carbonates, bicarbonates, and the like. Such bases useful in preparing the salts of this invention thus include sodium hydroxide, potassium hydroxide, ammonium hydroxide, potassium carbonate, sodium carbonate, sodium bicarbonate, potassium bicarbonate,

calcium hydroxide, calcium carbonate, and the like. The potassium and sodium salt forms are particularly preferred.

It should be recognized that the particular counterion forming a part of any salt of this invention is not of a critical nature, so long as the salt as a whole is pharmacologically acceptable and as long as the counterion does not contribute undesired qualities to the salt as a whole.

Preferred compounds of this invention are those compounds



where:

a is 0, 1 or 2;

each R is independently hydrogen, halo, C_1-C_4 alkyl, C_1-C_4 alkoxy or di(C_1-C_4)alkylamino;

R^0 is hydrogen;

R^2 is amino;

R^3 is dimethylamino, C_1-C_6 alkyl, halo(C_1-C_6)alkyl, phenyl, substituted phenyl, C_3-C_7 cycloalkyl, substituted C_3-C_7 cycloalkyl, thienyl, thiazolidinyl, pyrrolidino, piperidino or morpholino;

R^4 is hydrogen, methyl or ethyl;

R^5 is hydrogen, methyl or ethyl;

or a pharmaceutically acceptable salt thereof.

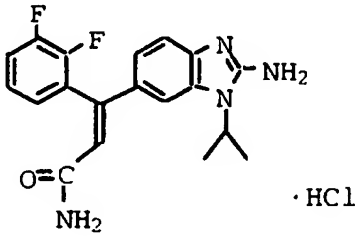
Of these preferred compounds, more preferred are those compounds of formula I where:

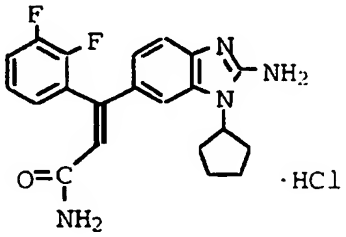
a is 0 or 1;

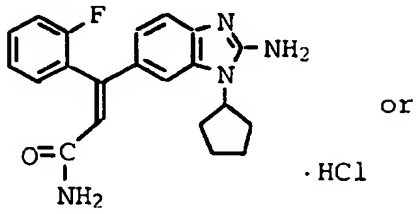
each R is independently hydrogen, fluoro, methyl, ethyl, methoxy, ethoxy, dimethylamino;

R^3 is C_1-C_4 alkyl, phenyl, substituted phenyl, C_3-C_7 cycloalkyl or substituted C_3-C_7 cycloalkyl;
or a pharmaceutically acceptable salt thereof.

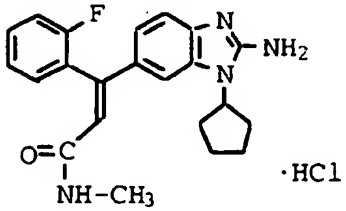
Of these compounds, the most preferred compounds are:







or



or a pharmaceutically acceptable salt thereof.

The compounds of formula I may be prepared by reacting a suitably substituted acetamide with a base to provide the corresponding anion which is then reacted with a suitably substituted ketone of formula IA to provide a carbinol intermediate. The reactions are typically carried out in an organic solvent for one to twelve hours at a temperature of

from about -90°C to room temperature using an excess of the base and acetamide reactant relative to the ketone reactant. The acetamide is preferably protected with a suitable protecting group prior to use in the reaction. Typical bases include sodium hydride, lithium diisopropylamide (LDA) and n-butyllithium. A preferred base is n-butyllithium. Solvent choice is not critical so long as the solvent employed is inert to the ongoing reaction and the reactants are sufficiently solubilized to effect the desired reaction. A solvent that is suitable for use in this reaction is tetrahydrofuran although the acetamide reactant can also be used as a solvent. The carbinol intermediate is generally prepared in from about one to eighteen hours when the reaction is initiated at -78°C and allowed to slowly warm to room temperature. The reaction may be monitored by HPLC and quenched by the addition of an acid when it is substantially complete. Typical acids include hydrochloric acid, hydrobromic acid, formic acid and the like. A preferred acid is concentrated hydrochloric acid. The resultant carbinol intermediate is preferably dehydrated without prior isolation or purification.

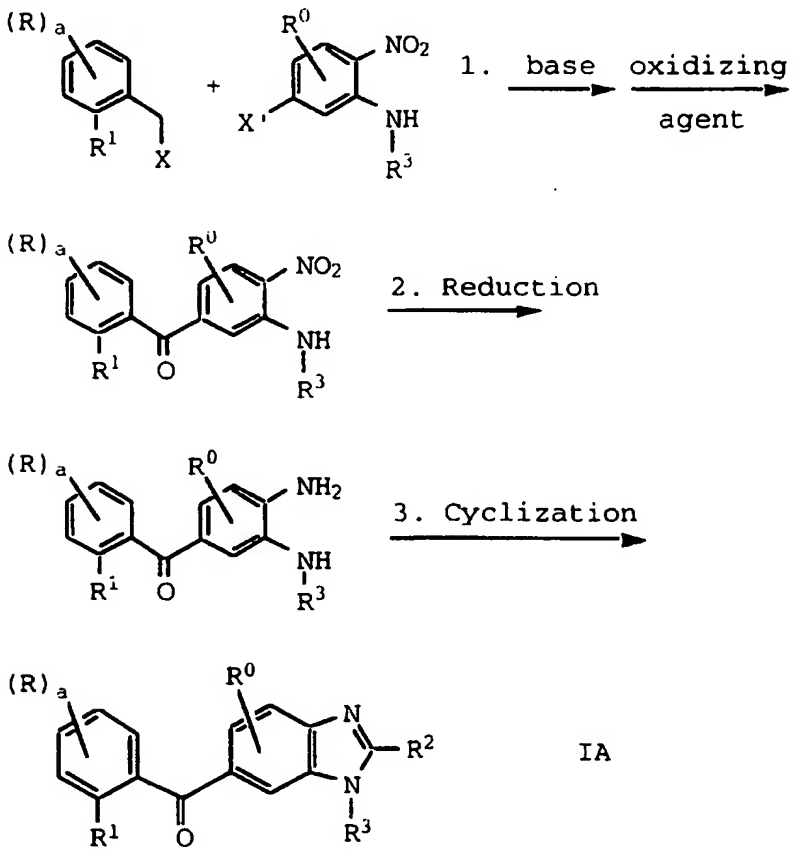
In particular, the carbinol intermediate is reacted with an acid for thirty minutes to twelve hours at a temperature of from about room temperature to the reflux temperature of the mixture to provide the desired compound of formula I. Typical acids include hydrochloric acid, hydrobromic acid, formic acid, acetic acid and combinations of acids. A preferred acid combination is formic acid containing concentrated hydrochloric acid. The desired compound is generally prepared in from about thirty minutes to seven hours when the reaction is carried out at just below the reflux temperature of the mixture. The reaction is preferably monitored by HPLC, for example, to ensure that the reaction goes to completion.

The compounds of formula I are preferably isolated and the resulting cis/trans isomers separated using procedures known in the art. For example, the cis and trans forms of

the isolated compounds may be separated using column chromatography, for example reverse phase HPLC. The compounds may be eluted from the column using an appropriate ratio of acetonitrile and water or methanol and water. The cis form of the compound may be converted to a cis/trans mixture by exposure to hυ irradiation and recycled through the above-mentioned purification process.

The ketone intermediates of formula IA may be prepared according to procedures detailed in the art. For example, the ketone intermediates may be prepared according to the following Reaction Scheme I.

Reaction Scheme I



IA

where:

X is cyano or -COOR', where R' is C_1-C_4 alkyl;

X' is halo;

a, R, R^0, R^1, R^2 and R^3 are defined above.

Reaction Scheme I, above, is accomplished by carrying out reactions 1-4. Once a reaction is complete, the intermediate compound may be isolated, if desired, by procedures known in the art. For example, the compound may be crystallized and then collected by filtration, or the reaction solvent may be removed by extraction, evaporation or decantation. The intermediate compound may be further purified, if desired, by common techniques such as crystallization or chromatography over solid supports such as silica gel or alumina, before carrying out the next step of the reaction scheme.

Reaction I.1 is accomplished by first exposing an appropriately substituted halo-nitroaniline and an appropriately substituted phenylacetonitrile or benzoate to a base in an organic solvent for one to twenty four hours at a temperature of from about -10°C to about 40°C to provide a ketone precursor. The reaction is typically carried out using equimolar proportions of the reactants in the presence of two equivalents of the base. Typical bases include sodium hydride, potassium t-butoxide, lithium diisopropylamide (LDA). A preferred base is potassium t-butoxide. Examples of solvents suitable for use in this reaction include dimethylformamide, dimethylacetamide and the like. Solvent choice is not critical so long as the solvent employed is inert to the ongoing reaction and the reactants are sufficiently solubilized to effect the desired reaction. The ketone precursor is generally prepared in from about one to fifteen hours when the reaction is initiated at 0°C and allowed to progress at room temperature. The ketone precursor is preferably oxidized in the same reaction mixture without prior isolation or purification.

In particular, the ketone precursor is reacted with an oxidizing agent for 30 minutes to 15 hours at a temperature of from about 0°C to about 30°C to provide the corresponding

ketone compound. Typical oxidizing agents include hydrogen peroxide, oxygen and air. The oxygen and air are typically bubbled through the reaction mixture. A preferred oxidizing agent is hydrogen peroxide, preferably in a 30% solution. The ketone is generally prepared in from about thirty to five hours when the reaction is carried out between 0°C and room temperature. The reaction is preferably monitored by TLC, for example, to ensure that the reaction goes to completion.

In reaction I.2, the nitro substituent on the ketone is reduced according to procedures known in the art to provide the corresponding diaminobenzophenone compound. For example, the nitro substituent may be reduced by catalytic hydrogenation, for example by combining the ketone isolated from reaction I.1 with hydrogen gas in ethanol or tetrahydrofuran and a catalyst. A preferred catalyst is palladium-on-carbon or Raney nickel. Solvent choice is not critical so long as the solvent employed is inert to the ongoing reaction and the nitro reactant is sufficiently solubilized to effect the desired reaction. The hydrogen gas is typically used at a pressure of up to 60 psi, preferably at or about 30 psi. The reaction is generally substantially complete after about 1 to 24 hours when conducted at a temperature in the range of from about 0°C to about 40°C. The reaction is preferably conducted at a temperature in the range of from about 20°C to about 30°C for about 2 to 5 hours.

In reaction I.3, the compound isolated from reaction I.3 is cyclized via a nitrile intermediate by reacting the benzophenone compound with cyanogen bromide in an alcoholic solvent such as isopropanol. Typically, the reaction is carried out at a temperature of from about 0°C to about 30°C. When the benzophenone is completely dissolved, the resultant solution is combined with cyanogen bromide. The cyanogen bromide is typically added in the form of a solution (3-7M for example in acetonitrile). The reaction is generally complete after one to eighteen hours when the

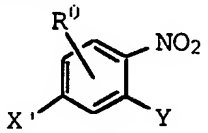
reaction mixture is stirred at room temperature. However, in certain instances nitrile intermediate will precipitate out of the reaction mixture. In order to form the desired ketone, this precipitate is isolated and then refluxed in an alcoholic solvent such as isopropanol for one to four hours to provide the desired ketone compound of formula I.

The compounds of the formula:

where:

X', R^0 and R^3 are as defined above;

are prepared by displacing the chloro or fluoro substituent on a compound of the formula



where Y is chloro or fluoro, with the proviso that Y cannot be chloro when X' is fluoro, with a primary amine of the formula NH_2R^3, where R^3 is as defined above, in an organic solvent. The reaction is optionally carried out in the presence of an acid scavenger such as potassium carbonate or a large excess of the primary amine. Typical solvents include tetrahydrofuran, dimethylformamide, dimethylacetamide and the like. The reaction is generally complete in one to twenty hours when carried out at a temperature of from about 20°C to about 80°C. The resultant alkylated halo nitroaniline is then reacted as described in Reaction Scheme I, above.

The compounds of formula I where R^2 is -NHC(O)(C_1-C_6 alkyl) may be prepared by acylating the ketone intermediate or the corresponding compound of formula I, where R^2 is amino, according to procedures known in the art. For example, the amine compound may be acylated with a suitable acyl halide, isocyanate or chloroformate, preferably in the presence of an acid scavenger such as a tertiary amine,

preferably triethylamine. A preferred acylating agent is acetic anhydride. The reaction is typically carried out at a temperature of from about -20°C to about 25°C. Typical solvents for this reaction include ethers and chlorinated hydrocarbons, preferably diethylether, chloroform or methylene chloride. The amine reactant is generally employed in equimolar proportions relative to the acylating reactant, and preferably in the presence of equimolar quantities of an acid scavenger such as a tertiary amine. A preferred acid scavenger for this reaction is N-methylmorpholine (NMM).

The compounds employed as initial starting materials in the synthesis of the compounds of this invention are known in the art, and, to the extent not commercially available are readily synthesized by standard procedures commonly employed in the art.

It will be understood by those in the art that in performing the processes described above it may be desirable to introduce chemical protecting groups into the reactants in order to prevent secondary reactions from taking place. Any amine, alcohol, alkylamine or carboxy groups which may be present on the reactants may be protected using any standard amino-, alcohol- or carboxy- protecting group which does not adversely affect the remainder of the molecule's ability to react in the manner desired. The various protective groups may then be removed simultaneously or successively using methods known in the art.

The pharmaceutically acceptable salts of the invention are typically formed by reacting a compound of formula I with an equimolar or excess amount of acid or base. The reactants are generally combined in a mutual solvent such as diethyl ether, tetrahydrofuran, methanol, ethanol, isopropanol, benzene and the like, for acid addition salts, or water, an alcohol or a chlorinated solvent such as methylene chloride for base addition salts. The salts normally precipitate out of solution within about one hour

to about ten days and can be isolated by filtration or other conventional methods.

The following Preparations and Examples further illustrate specific aspects of the present invention. It is to be understood, however, that these examples are included for illustrative purposes only and are not intended to limit the scope of the invention in any respect and should not be so construed.

In the following Preparations and Examples, the terms melting point, nuclear magnetic resonance spectra, electron impact mass spectra, field desorption mass spectra, fast atom bombardment mass spectra, infrared spectra, ultraviolet spectra, elemental analysis, high performance liquid chromatography, and thin layer chromatography are abbreviated "m.p.", "NMR", "EIMS", "MS(FD)", "MS(FAB)", "IR", "UV", "Analysis", "HPLC", and "TLC", respectively. The MS(FD) data is presented as the mass number unless otherwise indicated. In addition, the absorption maxima listed for the IR spectra are only those of interest and not all of the maxima observed.

In conjunction with the NMR spectra, the following abbreviations are used: "s" is singlet, "d" is doublet, "dd" is doublet of doublets, "t" is triplet, "q" is quartet, "m" is multiplet, "dm" is a doublet of multiplets and "br.s", "br.d", "br.t", and "br.m" are broad singlet, doublet, triplet, and multiplet respectively. "J" indicates the coupling constant in Hertz (Hz). Unless otherwise noted, NMR data refers to the free base of the subject compound.

The NMR spectra were obtained on a Brüker Corp. 250 MHz instrument or on a General Electric QE-300 300 MHz instrument. The chemical shifts are expressed in delta, δ values (parts per million downfield from tetramethylsilane). The MS(FD) spectra were taken on a Varion-MAT 731 Spectrometer using carbon dendrite emitters. EIMS spectra were obtained on a CEC 21-110 instrument from Consolidated Electrodynamics Corporation. IR spectra were obtained on a

Perkin-Elmer 281 instrument. UV spectra were obtained on a Cary 118 instrument. TLC was carried out on E. Merck silica gel plates. Melting points are uncorrected.

Example 1

A. 2-Isopropylamino-4-fluoro-nitrobenzene

To a cold (0°C) mixture of 43.35 ml (400 mmol) of 2,4-difluoronitrobenzene and 55 g (approx. 400 mmol) of potassium carbonate in 400 ml of tetrahydrofuran, was added approximately 34.4 ml of isopropylamine (400 mmol). The reaction mixture was warmed to room temperature and reacted for 60 hours and then filtered. The potassium carbonate was washed with ethyl acetate and the organics were then concentrated in vacuo resulting in the crystallization of the desired compound which was then isolated by filtration and washed with a small volume of hexane.
Yield: 66.37 g, yellow crystals (84%).

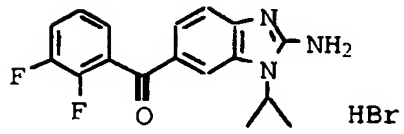
B. 3-Isopropylamino-4-nitro-2',3'-difluorobenzophenone

To a cold (0°C) mixture of 7.65 g (50 mmol) of 2,3-difluorophenylacetonitrile and 9.9 g (50 mmol) of the compound of Example 1A in 80 ml of dimethylformamide, was added 11.22 g (100 mmol) of potassium t-butoxide. The reaction mixture was warmed to room temperature and reacted for approximately 1 hour. When the reaction was substantially complete, as determined by TLC, the mixture was cooled to 0°C, followed by the addition of 15 ml of a 30% solution of hydrogen peroxide. The mixture was warmed to room temperature, stirred overnight and then poured into 1 liter of 1N hydrochloric acid resulting in the formation of 16 g of an orange solid which was used without further purification.

C. 3-Isopropylamino-4-amino-2',3'-difluorobenzophenone

The compound of Example 1B was hydrogenated in 250 ml of tetrahydrofuran using 2.1 g of Raney nickel catalyst under 60 psi of hydrogen (gas) for six hours. The reaction

mixture was filtered and the filtrate was concentrated in vacuo to provide 14 g of a solid which was used without further purification.

D. 

To a cold (0°C) mixture of 14 g of Example 1C in 125 ml of isoproyl alcohol, was added one equivalent of cyanogen bromide (9.6 ml of a 5M solution in acetonitrile). The resultant mixture was warmed to room temperature and stirred for 2 days and then concentrated in vacuo to provide a residue. This residue was redissolved in ethyl acetate and then sonicated resulting in the formation of 13.0 g of crystals.

Analysis for $C_{17}H_{16}N_3OBrF_2$:

Calcd: C, 51.53; H, 4.07; N, 10.61; Br, 20.17;

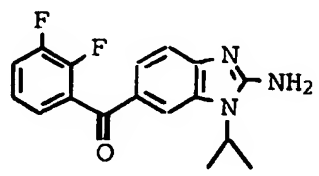
Found: C, 51.64; H, 4.17; N, 10.51; Br, 20.41.

MS(FD): 315 (M^+).

^1H NMR (300 MHz; d_6-DMSO): δ 1.56 (d, 6H); 4.85 (septet, 1H); 7.41 (m, 2H); 7.33 (d, 1H); 7.67 (d, 1H); 7.74 (m, 1H); 8.01 (s, 1H) and 8.87 (s, 2H).

IR($CHCl_3$): υ 3088, 2984, 1663, 1626, 1481, 1304 and 1276 cm^{-1}.

UV/VIS (95% EtOH): λ_{max} = 318 nm (E=11480); 223 nm (E=24524).

E. 

The desired compound was obtained by adding 1N sodium hydroxide to Example 1D in ethyl acetate. The resulting

layers were separated and the organic phase was concentrated in vacuo.

Yield: 9.34 g (62%).

Analysis for $C_{17}H_{15}N_3OF_2$:

Calcd: C, 64.76; H, 4.80; N, 13.33;

Found: C, 64.97; H, 4.78; N, 13.40.

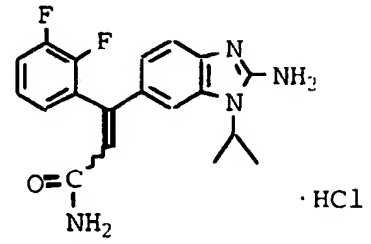
MS(FD): 315 (M^+).

^1H NMR (300 MHz; d_6-DMSO): δ 1.38 (d, 6H); 3.67 (septet, 1H); 7.01 (s, 2H); 7.18 (d, 1H); 7.35 (m, 3H); 7.66 (s, 1H) and 7.77 (s, 1H).

IR($CHCl_3$): υ 3380, 2910, 1652, 1608, 1522, 1307, 1276 and 1264 cm^{-1}.

UV/VIS (95% EtOH): λ_{max} = 341 nm (E=21011); 220.5 nm (E=26966).

F.



To a cold (-78°C) solution of 18.8 ml (76 mmol) of bis(trimethylsilyl)acetamide in 200 ml of tetrahydrofuran, was slowly added 30.4 ml of 2.5M n-butyllithium in hexane (76 mmol), followed by the addition of 3.0 g (9.5 mmol) of of Example 1E. The reaction mixture was stirred for 8 hours at -78°C and then allowed to warm to room temperature. When the reaction was substantially complete, as indicated by HPLC, the reaction was quenched by the addition of 6.4 ml (76 mmol) of concentrated hydrochloric acid and then concentrated in vacuo to provide an oil which was then redissolved in formic acid containing 1% concentrated hydrochloric acid. The mixture was allowed to react for 4 hours at 95°C. When the reaction was substantially complete, as indicated by HPLC, the mixture was concentrated in vacuo to provide an oil. This oil was separated using

reverse phase HPLC (eluent of acetonitrile in water) to provide the cis and trans isomers of the subtitled compound.

cis

not characterized

trans

Analysis for $C_{19}H_{21}N_4O_2F_2Cl$:

Calcd: C, 55.55; H, 5.15; N, 13.64;

Found: C, 54.21; H, 4.93; N, 12.98.

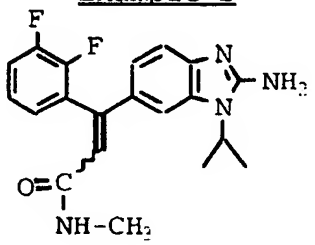
MS(FD): 356 (M^+).

^{1}H NMR (300 MHz; d_6-DMSO): δ 1.48 (d, 6H); 4.73 (septet, 1H); 6.71 (s, 1H); 7.93 (m, 3H); 7.18 (m, 2H); 7.25 (d, 1H); 7.35 (m, 1H); 7.42 (s, 1H); 7.52 (s, 1H); 7.79 (s, 2H).

IR (KBr): υ 3152, 2982, 1662, 1596, 1483, 1474 and 1269 cm^{-1}.

UV/VIS (95% EtOH): λ_{max} = 310 nm (E=9665); 223 nm (E=24308).

Example 2



The compound was prepared substantially as described in Example 1F using N-methyl-N-trimethylsilylacetamide.

cis

not characterized

trans

Analysis for $C_{20}H_{23}N_4O_2F_2Cl$:

Calcd: C, 56.54; H, 5.46; N, 13.19;

Found: C, 56.32; H, 5.10; N, 13.06.

MS(FD): 370.3 (M^+).

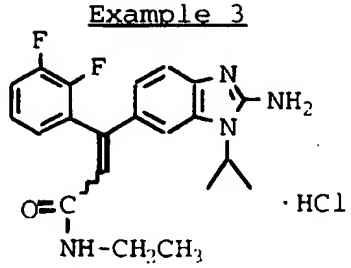
^{1}H NMR (300 MHz; d_6-DMSO): δ 2.52 (d, 6H); 2.59 (d, 3H); 4.81 (septet, 1H); 6.78 (s, 1H); 6.94 (m, 2H); 7.2 (m,

1H); 7.4 (m, 2H); 7.6 (s, 1H); 8.19 (m, 1H); 8.75 (m, 1H); 8.79 (s, 1H).

IR (KBr): υ 3068, 1669, 1627, 1589, 1482 and 1474 cm^{-1}.

UV/VIS (95% EtOH): λ_{max} = 305 nm (E=13688); 223 nm (E=30904).

Example 3



The compound was prepared substantially in accordance with Example 1E, with the exception that n-butyllithium (15.85 mmol) was slowly added to a solution that was prepared as follows. A cold (-78°C) solution of bis(trimethylsilyl)amide (1 equivalent) and N-ethylacetamide (1 equivalent) in tetrahydrofuran was stirred for 1 hour followed by the addition of chlorotrimethylsilane (1 equivalent). The resultant solution was stirred for 15 minutes and then allowed to warm slowly to room temperature. NOTE: The solution was cooled to -78°C again before the addition of the n-butyllithium.

cis

not characterized

trans

Analysis for $C_{21}H_{22}N_4OF_2 \cdot HCl \cdot H_2O$:

Calcd: C, 57.47; H, 5.74; N, 12.76;

Found: C, 57.25; H, 5.65; N, 12.74.

MS(FD): 384.2 (M^+).

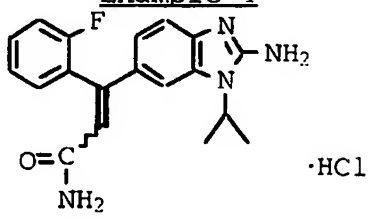
^1H NMR (300 MHz; d_6-DMSO): δ 0.96 (t, 3H); 1.49 (d, 6H); 3.0 (p, 2H); 4.80 (septet, 1H); 6.74 (s, 1H); 6.88 (t, 1H); 6.94 (d, 1H); 7.16 (q, 1H); 7.30-7.44 (m, 2H); 7.55 (s, 1H); 8.17 (t, 1H); 8.75 (s, 2H); and 12.8 (s, 1H).

IR ($CHCl_3$): υ 2986, 1664, 1602, 1514 and 1482 cm^{-1}.

UV/VIS (95% EtOH): λ_{max} = 304.00 nm (E=13407.11); 224.00 nm (E=31891.73).

The following compounds were prepared substantially as described in Example 1A-F.

Example 4



cis

MS(FD): 338 (M^+).

Analysis for $C_{19}H_{19}N_4OF \cdot HCl$:

Calcd: C, 60.88; H, 5.38; N, 14.95;

Found: C, 60.62; H, 5.66; N, 14.78.

trans

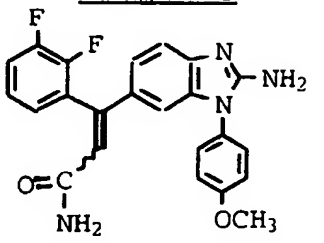
MS(FD): 338 (M^+).

Analysis for $C_{19}H_{19}N_4OF \cdot HCl \cdot 1.2H_2O$:

Calcd: C, 57.56; H, 5.70; N, 14.13;

Found: C, 57.26; H, 5.28; N, 13.75.

Example 5



cis

Analysis for $C_{23}H_{18}N_4O_2F_2$:

Calcd: C, 65.71; H, 4.32; N, 13.33;

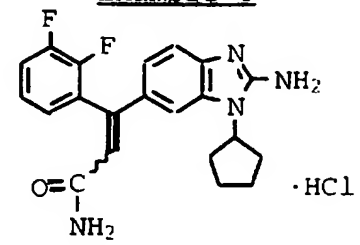
Found: C, 65.44; H, 4.30; N, 13.05.

MS(FD): 420 (M^+).

^{1}H NMR (250 MHz; d_6-DMSO): δ 3.83 (s, 3H); 6.08 (s, 1H); 6.29 (s, 2H); 6.78 (m, 2H); 7.13 (m, 6H); 7.33 (m, 4H).
IR ($CHCl_3$): υ 3390, 3013, 1664, 1514 and 1254 cm^{-1}.
UV/VIS (95% EtOH): λ_{max} = 217 nm (E=40891).

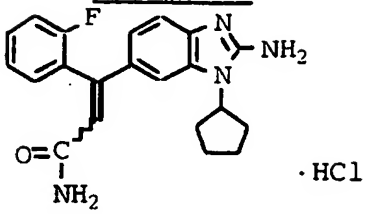
trans
Analysis for $C_{23}H_{18}N_4O_2F_2$:
Calcd: C, 65.71; H, 4.32; N, 13.33;
Found: C, 63.22; H, 4.63; N, 12.63.
MS(FD): 420 (M^+).
^{1}H NMR (250 MHz; d_6-DMSO): δ 3.86 (s, 3H); 6.40 (s, 2H); 6.49 (s, 1H); 6.71 (d, 1H); 6.84 (m, 3H); 7.13 (m, 4H); 7.32 (m, 3H) and 7.36 (d, 1H).
IR (KBr): υ 3416, 3314, 3201, 1664, 1582, 1543, 1513 and 1271 cm^{-1}.
UV/VIS (95% EtOH): λ_{max} = 330 nm (E=16300); 226 nm (E=33818).

Example 6



cis
not characterized
trans
MS(FD): 382 (M^+).
Analysis for $C_{21}H_{20}N_4OF_2 \cdot HCl \cdot 1.2H_2O$:
Calcd: C, 57.26; H, 5.35; N, 12.72;
Found: C, 57.21; H, 5.08; N, 12.47.

Example 7



·HCl

cis

MS(FD): 364 (M^+).

Analysis for $C_{21}H_{21}N_4OF \cdot 1.2HCl$:

Calcd: C, 61.79; H, 5.48; N, 13.73;

Found: C, 61.68; H, 5.60; N, 13.56.

trans

MS(FD): 364 (M^+).

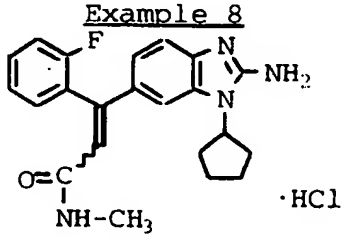
Analysis for $C_{21}H_{21}N_4OF \cdot HCl$:

Calcd: C, 62.92; H, 5.53; N, 13.98;

Found: C, 62.78; H, 5.55; N, 13.68.

The following compounds were prepared substantially as described above in Example 2.

Example 8



·HCl

cis

MS(FD): 378 (M^+).

Analysis for $C_{22}H_{23}N_4OF \cdot HCl \cdot 0.5H_2O$:

Calcd: C, 62.33; H, 5.94; N, 13.22;

Found: C, 62.33; H, 5.74; N, 12.98.

trans

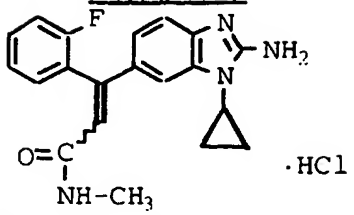
MS(FD): 378 (M^+).

Analysis for $C_{22}H_{23}N_4OF \cdot HCl \cdot 0.2H_2O$:

Calcd: C, 63.14; H, 5.88; N, 13.39;

Found: C, 63.00; H, 5.92; N, 13.33.

Example 9



cis

MS(FD): 350 (M^+).

Analysis for $C_{20}H_{19}N_4OF \cdot 1.5HCl \cdot 1.5H_2O$:

Calcd: C, 55.59; H, 5.48; N, 12.97;

Found: C, 55.92; H, 5.24; N, 12.80.

trans

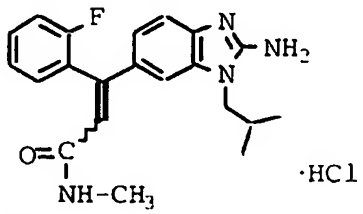
MS(FD): 350 (M^+).

Analysis for $C_{20}H_{19}N_4OF \cdot 1.6HCl$:

Calcd: C, 58.77; H, 5.08; N, 13.71;

Found: C, 58.89; H, 5.42; N, 12.55.

Example 10



cis

not characterized

trans

MS(FD): 366 (M^+).

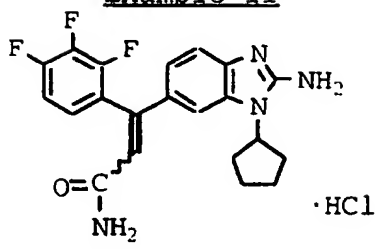
Analysis for $C_{21}H_{23}N_4OF \cdot 1.4HCl$:

Calcd: C, 60.42; H, 5.89; N, 13.42;

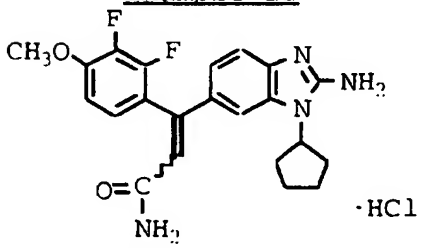
Found: C, 60.28; H, 6.15; N, 13.24.

The following compounds are made substantially as detailed in Example 1A-F.

Example 11



Example 12



The present compounds appear to inhibit replication of plus-strand viral RNA by interfering with the structure and/or function of the viral replication complex (a membrane-bound complex of viral and cellular proteins). Mutant rhinovirus and enterovirus have been isolated which demonstrate very low levels of drug tolerance. These mutants contain a single amino acid substitution in the protein that is expressed by the viral gene known as "3A". Therefore, the compounds of the present invention inhibit the rhinovirus and enterovirus by inhibiting a 3A function. The 3A gene encodes a hydrophobic protein which serves as the scaffolding protein that attaches the proteins of the replication complex to intracellular membranes.

The replicative strategy of flaviviruses such as hepatitis C virus (HCV) and bovine diarrheal virus (BVDV) is similar to that of the rhinovirus and enterovirus, discussed above. In particular, both families of virus contain single-stranded, messenger-sense RNA that replicates in a cytoplasmic complex via a minus-strand RNA intermediate. In

addition, both families of virus translate their genome into a polyprotein that is subsequently cleaved. Furthermore, the replication complexes of both viruses are tightly associated with intracellular membranes. Finally, both families of virus have analogous genomic structures including the presence of a 5' and 3' non-translated region which are required by the viruses for replication. There are two HCV proteins that have been implicated with this intracellular association: NS2 and NS4. It is postulated that either NS2 or NS4 is analogous to the picornavirus 3A protein.

Accordingly, another embodiment of the present invention is a method of treating or preventing a flavivirus infection comprising administering to a host in need thereof an effective amount of a compound of formula I or a pharmaceutically acceptable salt thereof. It is preferred to inhibit hepatitis C.

As noted above, the compounds of the present invention are useful as antiviral agents. They have shown inhibitory activity against various enterovirus and rhinovirus. An embodiment of the present invention is a method of treating or preventing a picornavirus infection comprising administering to a host in need thereof an effective amount of a compound of formula I or a pharmaceutically acceptable salt thereof.

The term "effective amount" as used herein, means an amount of a compound of formula I which is capable of inhibiting viral replication. The picornavirus inhibition contemplated by the present method includes either therapeutic or prophylactic treatment, as appropriate. The specific dose of compound administered according to this invention to obtain therapeutic or prophylactic effects will, of course, be determined by the particular circumstances surrounding the case, including, for example, the compound administered, the route of administration, the condition being treated and the individual being treated. A

typical daily dose will contain a dosage level of from about 0.01 mg/kg to about 50 mg/kg of body weight of an active compound of this invention. Preferred daily doses generally will be from about 0.05 mg/kg to about 20 mg/kg and ideally from about 0.1 mg/kg to about 10 mg/kg.

The compounds can be administered by a variety of routes including oral, rectal, transdermal, subcutaneous, intravenous, intramuscular and intranasal. The compounds of the present invention are preferably formulated prior to administration. Therefore, another embodiment of the present invention is a pharmaceutical formulation comprising an effective amount of a compound of formula I or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier, diluent or excipient therefor.

The active ingredient in such formulations comprises from 0.1% to 99.9% by weight of the formulation. By "pharmaceutically acceptable" it is meant that the carrier, diluent or excipient is compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

The present pharmaceutical formulations are prepared by known procedures using well-known and readily available ingredients. In making the compositions of the present invention, the active ingredient will usually be admixed with a carrier, or diluted by a carrier, or enclosed within a carrier which may be in the form of a capsule, sachet, paper or other container. When the carrier serves as a diluent, it may be a solid, semi-solid or liquid material which acts as a vehicle, excipient or medium for the active ingredient. Thus, the compositions can be in the form of tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, aerosols, (as a solid or in a liquid medium), ointments containing, for example, up to 10% by weight of the active compound, soft and hard gelatin capsules, suppositories,

sterile injectable solutions, sterile packaged powders and the like.

The following formulation examples are illustrative only and are not intended to limit the scope of the invention in any way. The term "active ingredient" means a compound according to formula I or a pharmaceutically acceptable salt thereof.

Formulation 1

Hard gelatin capsules are prepared using the following ingredients:

	Quantity (mg/capsule)
Active ingredient	250
Starch, dried	200
Magnesium stearate	10
Total	460 mg

Formulation 2

A tablet is prepared using the ingredients below:

	Quantity (mg/capsule)
Active ingredient	250
Cellulose, microcrystalline	400
Silicon dioxide, fumed	10
Stearic acid	5
Total	665 mg

The components are blended and compressed to form tablets each weighing 665 mg.

Formulation 3

An aerosol solution is prepared containing the following components:

	Weight
Active ingredient	0.25
Methanol	25.75
Propellant 22 (Chlorodifluoromethane)	70.00
Total	100.00

The active compound is mixed with ethanol and the mixture added to a portion of the propellant 22, cooled to -30°C and transferred to a filling device. The required amount is then fed to a stainless steel container and diluted with the remainder of the propellant. The valve units are then fitted to the container.

Formulation 4

Tablets, each containing 60 mg of active ingredient, are made as follows:

	Quantity (mg/tablet)
Active ingredient	60
Starch	45
Microcrystalline cellulose	35
Polyvinylpyrrolidone (as 10% solution in water)	4
Sodium carboxymethyl starch	4.5
Magnesium stearate	0.5
Talc	1
Total	150

The active ingredient, starch and cellulose are passed through a No. 45 mesh U.S. sieve and mixed thoroughly. The aqueous solution containing polyvinylpyrrolidone is mixed with the resultant powder, and the mixture then is passed through a No. 14 mesh U.S. sieve. The granules so produced are dried at 50°C and passed through a No. 18 mesh U.S. sieve. The sodium carboxymethyl starch, magnesium stearate

and talc, previously passed through a No. 60 mesh U.S. sieve, are then added to the granules which, after mixing, are compressed on a tablet machine to yield tablets each weighing 150 mg.

Formulation 5

Capsules, each containing 80 mg of active ingredient, are made as follows:

	Quantity (mg/capsule)
Active ingredient	80 mg
Starch	59 mg
Microcrystalline cellulose	59 mg
Magnesium stearate	2 mg
Total	200 mg

The active ingredient, cellulose, starch and magnesium stearate are blended, passed through a No. 45 mesh U.S. sieve, and filled into hard gelatin capsules in 200 mg quantities.

Formulation 6

Suppositories, each containing 225 mg of active ingredient, are made as follows:

Active ingredient	225 mg
Saturated fatty acid glycerides	2,000 mg
Total	2,225 mg

The active ingredient is passed through a No. 60 mesh U.S. sieve and suspended in the saturated fatty acid glycerides previously melted using the minimum heat necessary. The mixture is then poured into a suppository mold of nominal 2 g capacity and allowed to cool.

Formulation 7

Suspensions, each containing 50 mg of active ingredient per 5 ml dose, are made as follows:

Active ingredient	50 mg
Sodium carboxymethyl cellulose	50 mg
Syrup	1.25 ml
Benzoic acid solution	0.10 ml
Flavor	q.v.
Color	q.v.
Purified water to total	5 ml

The active ingredient is passed through a No. 45 mesh U.S. sieve and mixed with the sodium carboxymethyl cellulose and syrup to form a smooth paste. The benzoic acid solution, flavor and color are diluted with a portion of the water and added, with stirring. Sufficient water is then added to produce the required volume.

Formulation 8

An intravenous formulation may be prepared as follows:

Active ingredient	100 mg
Isotonic saline	1,000 ml

The solution of the above ingredients generally is administered intravenously to a subject at a rate of 1 ml per minute.

The following experiment was carried out to demonstrate the ability of the compounds of formula I to inhibit certain virus.

Test Method for Anti-picornaviral Assay

African green monkey kidney cells (BSC-1) or Hela cells (5-3) were grown in 25 cc Falcon flasks at 37°C in medium 199 with 5 percent inactivated fetal bovine serum (FBS), penicillin (150 units 1 ml) and streptomycin (150 micrograms per milliliter (μg/ml)). When confluent monolayers were formed, the supernatant growth medium was removed and 0.3 ml of an appropriate dilution of virus (echo, Mengo, Coxsackie, polio or rhinovirus) were added to each flask. After

absorption for one hour at room temperature, the virus infected cell sheet was overlaid with a medium comprising one part of 1 percent Ionagar No. 2 and one part double strength Medium 199 with FBS, penicillin and streptomycin which contains drug at concentrations of 100, 50, 25, 12, 6, 3 and 0 μg/ml. The flask containing no drug served as the control for the test. The stock solutions of vinyl acetylene benzimidazole compounds were diluted with dimethylsulfoxide to a concentration of 10^4 μg/ml. The flasks were then incubated for 72 hours at 37°C for polio, Coxsackie, echo and Mengo virus and 120 hours at 32°C for rhinovirus. Virus plaques were seen in those areas were the virus infected and reproduced in the cells. A solution of 10 percent formalin and 2 percent sodium acetate was added to each flask to inactivate the virus and fix the cell sheet to the surface of the flask. The virus plaques, irrespective of size, were counted after staining the surrounding cell areas with crystal violet. The plaque count was compared to the control count at each drug concentration. The activity of the test compound was expressed as percentage plaque reduction, or percent inhibition. Alternatively, the drug concentration which inhibits plaque formation by 50 percent can be used as a measure of activity. The 50 percent inhibition is indicated by the symbol IC50.

In vitro CPE/XTT anti-BVDV Assay

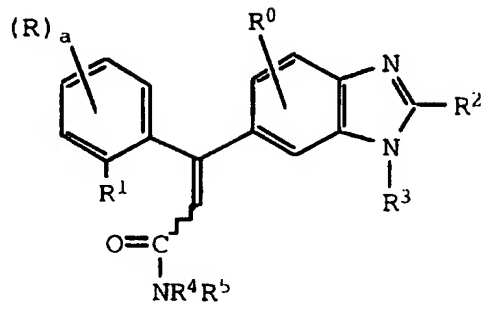
MDBK cells were dispersed in the 96-wells microtiter plate at 10,000 cells per well with Minimum Essential Medium containing Earl's balanced salt solution (EBSS), 2% horse serum, penicillin (100 units/ml) and streptomycin (100 μg/ml). Plates were grown at 37°C CO_2 incubator overnight. The MDBK cells were then infected with ~0.02 moi (multiplicity of infection) of bovine viral diarrhea virus (BVDV, ATCC VR-534). After allowing the virus to adsorb to the cells for 1-2 hours, medium containing serial dilutions of drug or medium alone was added to the wells. After

further incubating for 3-4 days (when extensive cpe was apparent in medium alone wells), the antiviral effect of testing drugs were assessed by performing a XTT assay as described below.

XTT [2,3-bis(methoxy-4-nitro-5-sulfophenyl)-2H-tetraazolium-5-carboxanilide, inner salt, sodium salt] at 1mg/ml for warm medium without FBS were freshly prepared and used immediately. For each 5 ml of the XTT solution, 25 µl of 5mM of PMS (phenazine methosulfate) in phosphate buffer saline was added. Then 50 µl of the freshly prepared XTT/PMS mixture was added to each of the microtiter wells. Incubate at 37°C (CO_2) for 3-4 hours or until color change is prominent. Read absorptance at 450 nm/ref. 650 nm in a spectrophotometer. The concentration of drug required to cause 50% cytotoxic effect as compared to the no drug no virus control (TC_{50}) and which to inhibit the development of virus cytopathic effect (cpe) by 50% (IC_{50}) was then determined from the liner portion of each dose response curve.

Claims

1. A compound of the formula I



I

wherein:

a is 0, 1, 2 or 3;

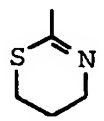
each R is independently hydrogen, halo, cyano, amino, halo(C_1-C_6)alkyl, di(C_1-C_4)alkylamino, azido, C_1-C_6 alkyl, carbamoyl, carbamoyloxy, carbamoylamino, C_1-C_6 alkoxy, C_1-C_4 alkylthio, C_1-C_4 alkylsulfinyl, C_1-C_4 alkylsulfonyl, pyrrolidino, piperidino or morpholino;

R^0 is hydrogen, halo, C_1-C_4 alkyl or C_1-C_4 alkoxy;

R^1 is halo, cyano, hydroxy, methyl, ethyl, methoxy, ethoxy, methylthio, methylsulfinyl or methylsulfonyl;

R^2 is hydrogen, amino or -NHC(O)(C_1-C_6 alkyl);

R^3 is dimethylamino, C_1-C_{10} alkyl, C_3-C_7 cycloalkyl, substituted C_3-C_7 cycloalkyl, halo(C_1-C_6)alkyl, phenyl, substituted phenyl, furyl, thienyl, thiazolyl, thiazolidinyl, pyrrolidino, piperidino, morpholino or a group of the formula:

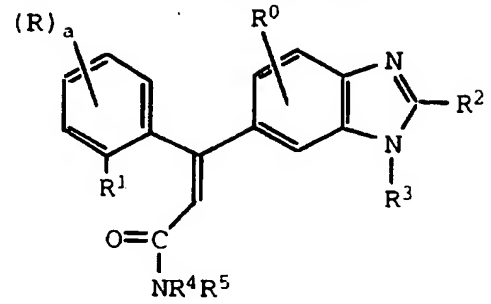


;

R^4 and R^5 are independently hydrogen or C_1-C_4 alkyl;

or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1



where:

a is 0, 1 or 2;

each R is independently hydrogen, halo, C_1-C_4 alkyl, C_1-C_4 alkoxy or di(C_1-C_4)alkylamino;

R^0 is hydrogen;

R^2 is amino;

R^3 is dimethylamino, C_1-C_6 alkyl, halo(C_1-C_6)alkyl, phenyl, substituted phenyl, C_3-C_7 cycloalkyl, substituted C_3-C_7 cycloalkyl, thienyl, thiazolidinyl, pyrrolidino, piperidino or morpholino;

R^4 is hydrogen, methyl or ethyl;

R^5 is hydrogen, methyl or ethyl;

or a pharmaceutically acceptable salt thereof.

3. A compound according to claim 2 where:

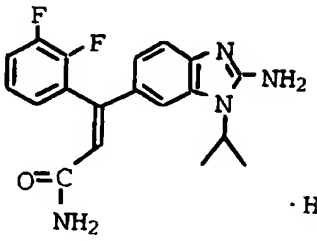
a is 0 or 1;

each R is independently hydrogen, fluoro, methyl, ethyl, methoxy, ethoxy, dimethylamino;

R^3 is C_1-C_4 alkyl, phenyl, substituted phenyl, C_3-C_7 cycloalkyl or substituted C_3-C_7 cycloalkyl;

or a pharmaceutically acceptable salt thereof.

4. A compound according to claim 3 which is:



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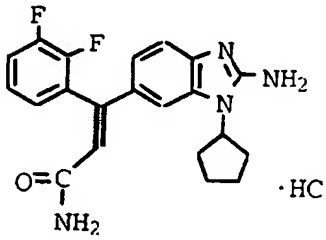

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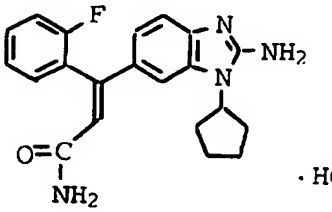

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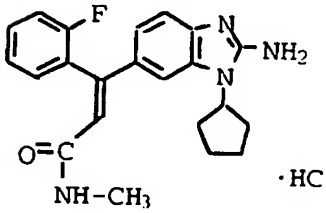

;

or a pharmaceutically acceptable salt thereof.

5. A pharmaceutical formulation comprising a compound of formula I, or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1 to 4, associated with one or more pharmaceutically acceptable carriers, diluents or excipients.

6. A compound of formula I, or a pharmaceutically acceptable salt thereof, a claimed in any one of claims 1 to 4, for use as a pharmaceutical.

7. A compound of formula I, or a pharmaceutically acceptable salt thereof, a claimed in any one of claims 1 to 4, for use as an antiviral.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/08848

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : A61K 31/415; C07D 235/30
US CL :514/388; 548/307.4
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/388; 548/307.4

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 4,420,479 A (MORWICK et al) 13 December 1983, see Examples 26-28.	1 - 3 , 5 - 7 , (parts), 4

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document published on or after the international filing date

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
23 JULY 1997	29 AUG 1997
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer R. W. RAMSUER Telephone No. (703) 308-1235

Form PCT/ISA/210 (second sheet)(July 1992)*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/08848

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 1-3,5-7(parts)
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

Please See Extra Sheet.

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/08848

BOX I. OBSERVATIONS WHERE CLAIMS WERE FOUND UNSEARCHABLE

2. Where no meaningful search could be carried out, specifically:

The multitude of variables and their permutations and combinations (e.g.a,R0,R1,R2,R3,etc.) result in claimed subject matter that is so broad in scope that it is rendered virtually incomprehensible and thus no meaningful search can be given. Note also that the claimed subject matter lacks a significant structural element qualifying as the special technical feature that clearly defines a contribution over the art. The subject matter claimed contains a phenyl aminocarbonylethylidene benzimidazole group which does not define a contribution over the prior art. Therefore, the first discernible invention (compounds)as found in Example 1 and the pharmaceutical composition therewith, has been searched.

CORRECTED VERSION*

PCT

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International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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A1

(11) International Publication Number: **WO 97/46237**

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(30) Priority Data:
60/019,170 5 June 1996 (05.06.96) US

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(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: ANTI-VIRAL COMPOUNDS

(57) Abstract

The present application provides a series of benzimidazole compounds which inhibit the growth of picornaviruses, such as rhinoviruses, enteroviruses, polioviruses, coxsackieviruses of the A and B groups, echo virus and Mengo virus and flaviviruses such as hepatitis C and bovine diarrheal virus.

* (Referred to in PCT Gazette No. 08/1998, Section II)

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